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Cumulative Risk Assessment Framework

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1.0 Executive Summary

This document describes the framework and methodology that Health Canada's Pest Management Regulatory Agency (PMRA) will use for assessing the cumulative effects of pesticides that have a common mechanism of toxicity. It supersedes Health Canada's 2001 Science Policy Note (SPN2001-01) on Guidance for Identifying Pesticides that have a Common Mechanism of Toxicity for Human Health Risk Assessment. The document also builds upon Health Canada's response to the Commissioner of the Environment and Sustainable Development 2015 audit on pesticide safety, whereby the PMRA indicated its intention to have methodology for cumulative assessment in place in the 2017-2018 fiscal year.[1] The document takes into account approaches taken by other chemical regulators and outlines general methods for cumulative risk assessment that are based on additive behaviors of these chemicals when combined. A step-wise approach for identifying pesticides that belong to a common mechanism group is presented including criteria for initial grouping and considerations for refining a common mechanism group. A flexible tiered framework for assessing the hazard and exposure components of an assessment is presented that will facilitate the refinement of these parameters in a cumulative risk assessment to the extent needed, thereby using resources efficiently. While the document summarizes elements of cumulative risk characterization, some of the uncertainties and challenges with respect to cumulative methodology in general are presented.

The PMRA will accept written comments on this proposal up to 45 days from the date publication of this document. Please forward all comments to Publications (please see contact information indicated on the cover page of this document).

2.0 Introduction

For the purpose of this policy, cumulative assessment is aimed at identifying the risks associated with co-exposures to two or more chemicals that cause a common toxic effect(s) by the same, or essentially the same, sequence of major biochemical events (that is, a common mechanism of toxicity). Concurrent exposure routes (oral, dermal, inhalation) and pathways (for example, diet, drinking water, residential use) to chemicals that share a common mechanism of toxicity are assessed to determine the potential for cumulative effects, based on the likelihood that people may be exposed to more than one of these chemicals at the same time. Cumulative assessment is undertaken to explore the possibility that low-level exposures to specific multiple chemicals could lead to the same or increased health risk relative to a higher level of exposure to any of these chemicals individually.

The consideration of the cumulative effects of pesticides was mandated in the modernization of Canadian pesticide legislation and reflects the application of modern science. Specifically, sections 7, 11 and 19 of the *Pest Control Products Act* (PCPA, 2006) requires the consideration of "available information on...cumulative effects of the pest control product and other pest control products that have a common mechanism of toxicity" in evaluating the health risks of a pesticide. In some scientific circles, exposure to multiple chemicals by multiple routes and pathways is referred to as combined exposure to multiple chemicals rather than cumulative

[1] http://www.hc-sc.gc.ca/cps-spc/pest/part/protect-proteger/pesticide-safety-securite-pesticide/index-eng.php

exposure; however, the terminology used through this document reflects that used in the PCPA for the assessment of pesticides. The scope of this policy does not extend to the consideration of mixtures of chemicals that may result in cumulative effects through disparate mechanisms of toxicity; however, it is worth acknowledging that this is an area of interest in the international regulatory community to be closely monitored.

Assessing the cumulative effects of pesticides to human health differs from aggregate assessment, which considers the risk from exposure (non-occupational) to a single chemical via all relevant routes and exposure pathways. Aggregate risk assessments have been fully implemented in the review of both new and re-evaluated pesticides and are supported by policy (Health Canada, 2003).

Currently, the PMRA is completing individual assessments for pesticides within the same common mechanism group through its re-evaluation program. It is essential that toxicological and exposure assessments of individual chemicals are up-to-date prior to undertaking the complex task of cumulative assessment. Cumulative assessments of pesticides that are known metabolites of one another (for instance, acephate and methamidophos) have been undertaken by the PMRA as the Agency continues to build its methods in this emerging area of science. The PMRA continuously monitors method development as well as specific cumulative assessments at the international level to determine their relevancy to the Canadian context.

This document sets out a framework to facilitate the assessment of cumulative risk of pesticides that share a common mechanism of toxicity. The framework is not intended to be prescriptive but rather is intended to function as a guide to those conducting cumulative assessments as well as a tool to communicate current practices to stakeholders. The document outlines general methods for cumulative risk assessment, considerations for identifying pesticides that belong to a common mechanism group, a tiered framework consisting of increasing levels of hazard and exposure refinement, elements of risk characterization and a discussion of uncertainties. The framework contained herein draws from efforts undertaken by other Health Canada programs, North American Free Trade Agreement (NAFTA) partners such as the United States Environmental Protection Agency (USEPA) and by international regulatory and scientific communities.

It is anticipated that by closely aligning the framework and methodology with that of other regulators, that PMRA can make use of cumulative assessments undertaken by those regulators, in whole or in part, provided that the assessments are relevant to the Canadian context.

3.0 Cumulative Risk Assessment Methods

In assessing the risk of chemicals with a common mechanism of toxicity, it is not necessary to have a full understanding of the entire molecular sequence of events required to produce a specific biological outcome. Rather, a more important aspect is having an understanding of the key cytological and biochemical events following chemical interaction. In this sense, the concept of mode of action, often used in cancer risk assessment, and generally considered to require less detail in the description of events than at the molecular level, is applicable. More recently, the term adverse outcome pathway has been employed to link the molecular initiating event(s) to

progressive levels of biological organization at the individual or population level. Mechanism of toxicity, mode of action and adverse outcome pathway are all conceptually similar constructs for establishing the key events that define a common mechanism group.

Fundamentally, exposure to more than one chemical at a time is required for there to be a cumulative effect. When combined, chemicals can act jointly, resulting in three distinct types of action: independent, as an interaction (that is synergistically or antagonistically) or in an additive manner. Chemicals that act independently typically do so through different modes of action and are referred to as complex mixtures. Independently-acting chemicals, by definition, are not addressed by cumulative assessment as mandated under current pesticide legislation.

Interactions refer to synergistic or antagonistic actions between or among chemicals. From a public health perspective, synergistic interactions are of concern as default assumptions of additivity could lead to an under-prediction of risk; however, synergistic interactions are quite rare. Data analysis suggests that when present, the magnitude of the under-prediction is relatively small (EC, 2009; EC 2012).

Chemicals that act via the same mode of action, referred to as simple mixtures when combined, can be characterized as behaving in an additive manner. The concept of dose or concentration addition assumes no chemical interactions, but acknowledges that the combination of effects will be greater than that of each individual chemical. For the purpose of cumulative assessment, as described herein, an additive action is the default assumption used by most regulatory authorities (USEPA, 2002; EFSA, 2008).

The most common dose/concentration addition approaches are the hazard index method, margin of exposure method or relative potency factor method. These methods are described herein in further detail. The choice of method used in a cumulative risk assessment will be influenced primarily by the context of the assessment, the available data and the level of refinement required in the assessment. The use of an alternate approach is not precluded but it is paramount that any alternate approach is scientifically defensible, well-documented and communicated in a transparent manner.

3.1 Hazard Index Method

The hazard index (HI) method is a simple and flexible approach that sums the individual hazard quotients (HQ) of individual chemicals in a cumulative assessment group. The HQ is the ratio of an individual chemical's exposure to its reference value. The reference value is the point of departure, (that is, the No Observed Adverse Effect level [NOAEL], Lowest Observed Adverse Effect level [LOAEL], or lower confidence limit on the benchmark dose [BMDL]), divided by the composite assessment factor (that is, the product of the uncertainty factors and the PCPA factor). The PCPA factor is a legally-mandated margin of safety intended to afford particular protection of infants and children (Health Canada, 2008). A HI index greater than 1 would indicate a potential health risk concern. It is worth emphasizing that the points of departure used in a cumulative risk assessment, using any method, may be different from those used in the risk assessment of an individual chemical given the focus on common effect.

$$HQ = \frac{\text{Exposure}}{\text{Reference Value}} \qquad \text{Reference Value} = \frac{\text{Point of Departure}}{\text{Composite Assessment Factor}}$$

$$HI = \frac{\text{Exposure}_1}{\text{Reference Value}_1} + \frac{\text{Exposure}_2}{\text{Reference Value}_2} \ ... + ... \ \frac{\text{Exposure}_n}{\text{Reference Value}_n}$$

The approach allows for the application of chemical-specific uncertainty factors regardless of whether they are applied for scientific reasons (such as the extrapolation of short-term data to a long-term scenario) or for policy considerations (such as the PCPA factor). It should be noted however, that the application of these uncertainty factors can mask the relative potency of the chemicals in a common mechanism group and thus, can inflate the overall uncertainty in the group.

3.2 Margin of Exposure (MOE) Method

The margin of exposure of a chemical is the ratio of its point of departure to its exposure. The adequacy of the MOE is determined by comparing it to a target MOE, the latter being an expression of the limitations (that is, the product of the uncertainty factors and the PCPA factor) associated with that chemical. The margin of exposure method (MOE_{Total}) calculates the reciprocal of the sum of the reciprocals of the MOEs of individual chemicals in a cumulative assessment group (see equation below). This method does not include consideration of the limitations associated with each individual assessment. Limitations associated with the common mechanism group at large are taken into account in determining the target MOE for the group. A potential health concern would be flagged if the MOE_{Total} is less than the target MOE or composite assessment factor (that is, the product of the uncertainty factors and the PCPA factor) for the group of chemicals.

$$MOE = \frac{\text{Point of Departure}}{\text{Exposure}}$$

$$MOE_{Total} = \frac{1}{\frac{1}{MOE_1} + \frac{1}{MOE_2} \ ... + ... \ \frac{1}{MOE_n}}$$

This method is currently used by the PMRA in conducting aggregate assessments of individual pesticides. The limitations of the database for each chemical in the assessment group are not quantified in this approach, but it remains a simple and flexible method to assess cumulative risk.

3.3 Relative Potency Factor Method

The relative potency method is a more complex approach that capitalizes on the occurrence of similar effects seen in chemicals with a common mechanism of action. This approach relies upon the selection of an index chemical within a cumulative assessment group, against which the other members of the group are compared. The index chemical should have a robust database and be

representative of the chemicals in the assessment group. The relative potency factor (RPF), or scaling factor, for each chemical is derived by dividing the point of departure for a common measure of effect for the index chemical, termed the effective dose (ED), by the point of departure for the same measure of effect for the individual chemical. For example, the effective dose of the index chemical that results in 10% response is compared to the effective dose of each test chemical in the assessment group that also results in a 10% response.

$$RPF_1 = \frac{ED_{index}}{ED_1}$$

In cases where the magnitude of the uncertainty factors is the same for each chemical of the assessment group, this magnitude would be reflected as the target MOE for the combined exposures (see Table 1, Example 1). In situations where the uncertainty factors vary among the chemicals, the relative potency factor for each chemical can be multiplied by the respective factor to yield an adjusted RPF (see Table 1, Example 2). Any factor used to adjust the RPF should not be double-counted in the target MOE for the combined exposures. For example, as illustrated in Table 1, Example 2, the uncertainty factor for interspecies extrapolation and the PCPA factor differs among the three chemicals. Therefore, the adjusted RPF for each chemical is calculated by multiplying the RPF by the chemical-specific uncertainty factor for interspecies extrapolation and PCPA factor. As the uncertainty factor for intraspecies variability for all three chemicals is the same (that is, 10-fold), and was not used to calculate the adjusted RPF, it forms the basis of the target MOE for the combined exposures.

Once the relative potency factor (adjusted or otherwise) for each individual chemical has been derived, exposures of these chemicals can be converted to an index chemical equivalent exposure (multiplying the chemical-specific exposure estimates by their respective RPF) and compared to the point of departure for the index chemical and the target MOE for the combined exposures.

Table 1 Examples of Uncertainty Factor Incorporation in RPF Methodology.

Chemical	RPF	UF_A	UF_H	PCPA	Adjusted RPF	Target MOE
Example 1						
Index Chemical A	1	10	10	1	-	100 ($UF_A \times UF_H \times$ PCPA)
Chemical B	2.5	10	10	1	-	
Chemical C	0.4	10	10	1	-	
Example 2						
Index Chemical X	1	10	10	1	10	10 (UF_H)
Chemical Y	3	3	10	1	9	
Chemical Z	0.01	10	10	3	0.3	

UF_A – uncertainty factor for interspecies extrapolation (that is, animal to human extrapolation)
UF_H – uncertainty factor for intraspecies variability (that is, within human variability)
PCPA – PCPA factor

The RPF approach provides a more refined method for standardizing the dose metrics for chemicals in an assessment group, but is heavily reliant on the quality and availability of appropriate toxicology data. Although it allows for the consideration of potency and uncertainties of individual chemicals, a limitation of the approach is the assumption of similarly shaped dose-response curves. This approach has been utilized by the USEPA in their cumulative assessment of various pesticide classes such as the organophosphates and N-methyl carbamates.

4.0 Selection Considerations for Common Mechanism Groups

A common mechanism of toxicity pertains to two or more chemicals that share a common toxic effect that results from the same, or essentially the same, sequence of major biochemical events. Care must be taken not to confuse mechanism of toxicity with site of toxic action. Likewise, for some chemicals, the site of toxic effect may be different than the site of toxic action. For instance, the anterior pituitary gland would be the site of toxic action for a chemical inhibiting the thyroid stimulating hormone (mechanism of toxicity) whereas the thyroid would be the site of toxic effect for the ensuing hypothyroidism. Another chemical could share the common toxic effect of hypothyroidism but have a different mechanism of toxicity such as the inhibition of thyroxine and triiodothyronine; in this case, the site of toxic effect and site of toxic action would be the same.

Many chemicals can cause more than one toxic effect, depending on the level of exposure, and do so by different mechanisms of toxicity at different sites of toxic action. However, a chemical may also cause multiple toxic effects at multiple sites from a single mechanism of toxicity taking place at a single site of toxic action. An example of the latter would be the downstream effects occurring from inhibiting the conversion of cholesterol to corticosteroid hormones in the adrenal cortex.

The PMRA follows a "weight-of-evidence" approach to support the development of hypotheses pertaining to mechanisms of toxicity. Generally, a single piece of information is insufficient on its own to support the characterization of a specific or common mechanism of toxicity; this finding will require support by the analysis and interrelationships of multiple pieces of information.

4.1 Preliminary Grouping

The process of cumulative assessment begins with identifying a preliminary grouping of chemicals that might cause a common toxic effect by a common mechanism of toxicity. This preliminary grouping of chemicals will be based upon at least one of the following criteria.

Structural similarity

It is assumed that chemicals that are structurally analogous could contain a common toxophore and may interact analogously with cellular molecular sites to cause a common toxic effect. This would also include any chemicals that are biotransformed by mammals to yield a common toxophore upon metabolism. Data on structure-activity relationships, quantitative structure-activity relationship modelling and structural alerts can contribute to the identification of structural analogs.

Similarity of mechanism of action

(a) General mechanism of toxicity in pests: the mechanisms by which some pesticides are toxic to humans can be fundamentally similar or, in some cases, identical to their mechanisms of intended toxicity to pests.

(b) General mechanism of mammalian toxicity: this is based on the possibility that chemicals that share a known general mechanism of toxicity may cause a common toxic effect. A general mechanism of toxicity may include, for example, chemicals that uncouple oxidative phosphorylation.

Similarity of toxic effect

It is possible that a particular toxic effect known to occur in experimental animals or humans could be common (that is , concordant in both site and nature) to many chemicals, and that this commonality in toxicity could be due to a common mechanism. Since this type of grouping is functionally based, not structurally based, it enables the identification of structurally unrelated chemicals that cause a common toxic effect from a common mechanism that otherwise might not be identifiable from groupings based on structural similarity or mode of pesticidal action alone.

Not all toxic effects can be used as a preliminary basis for grouping chemicals. Toxic effects that have many possible unrelated causes, or that could be defined as nonspecific in origin, are not appropriate as the primary basis for the initial grouping of chemicals. These effects, such as body weight changes or death, can result from many unrelated factors and are usually of limited value in understanding the mechanism of toxicity. Such generalized effects, therefore, will not typically be used as a basis for an initial grouping. The PMRA will group chemicals that cause multiple toxic effects by a common mechanism from a common site of toxic action for purposes of the preliminary grouping, provided at least one of the toxic effects is common among the chemicals.

Following the initial grouping of chemicals, a detailed evaluation of available toxicology data for each chemical will be undertaken to identify and characterize the toxic effects caused by each chemical, and to determine which of the chemicals cause toxic effects that are common with other chemicals (that is, toxic effects that are concordant in both site and nature). Toxicity data generated in support of regulatory submissions will be the primary source of information used by the PMRA. The PMRA may also use toxicity data obtained from other studies, such as those described in regulatory reports, or the published scientific literature. Chemicals may be placed in more than one group in instances where chemicals cause more than one common toxic effect.

The PMRA does not regard the preliminary grouping alone to reliably conclude that such chemicals have a common mechanism of toxicity. Hence, only those chemicals that cause a common toxic effect by a common mechanism (through the in-depth review described below) will be considered by the PMRA for cumulative risk assessment.

4.2 Refined Grouping

The next phase of the review process is to determine the mechanisms by which the chemicals of the preliminary group cause the common toxic effect(s). Once the critical biochemical/molecular events pertaining to toxicity are understood for each chemical, they can be compared and the identification of those chemicals that are toxic from a common mechanism can be made. The PMRA will base this assessment on previous Agency reviews, scientific literature, toxicity databases, and information from registrants, the EPA, or other regulatory authorities, ensuring that the mechanism is consistent with current toxicological theory and knowledge and deemed scientifically plausible by the PMRA for these purposes.

For those chemicals whose toxic mechanisms are not known or not well understood, or for which there is an absence of direct mechanistic data, the PMRA will analyze available structural data, pharmacokinetic data, and toxicity data of the pesticide, its toxophore, and its analogs. A weight-of-evidence approach will be undertaken to determine the major biochemical events that are most critical in causing toxicity. Mechanistic similarities that would support a finding of a common toxic mechanism include, for example, analogous interactions of the pesticide with identical or similar biological targets, and the occurrence of similar metabolic transformations that yield common or structurally analogous metabolites that interact with similar biological targets, or that are otherwise involved in causing toxicity. Chemicals that cause a common toxic effect by different mechanisms will be excluded from the refined grouping.

5.0 Cumulative Risk Assessment Framework

Once a refined common mechanism group has been established, the assessment of the cumulative exposures to the chemicals of that group will be undertaken. The PMRA supports the use of the WHO/IPCS framework to maximize efficiency in performing this task (Meek et al, 2011). The framework involves a tiered approach to the assessment of exposure and hazard, with each tier being more refined (that is, less conservative and uncertain) than the previous tier. As the tiers of assessment increase, the effort to perform the assessment generally increases as does the data required to support the refinements. The WHO/IPCS framework has also been employed by regulators responsible for Canada's Chemical Management Plan (Health Canada, Environment Canada, 2015). This iterative process is also similar to the screening analysis framework put forth by the USEPA (USEPA, 2015).

A conceptual representation of the framework, as constructed by WHO/IPCS, is presented in Appendix 1 and forms the foundation of the approach that the PMRA will take. The elements of the framework are not fixed and will vary depending on the available data. It is not necessary for the hazard and exposure components to be assessed at similar tiers of refinement; rather, the available data will dictate the extent to which either component can be refined. The risk assessor needs only to progress through the tiers to the point where risk does not exceed the level of concern; if unacceptable risk is still present with the maximal level of refinement, then regulatory action is warranted.

As part of the approach to conserving resources in assessment and focussing on critical areas, the PMRA will leverage assessments (or parts of assessments) from other jurisdictions that have

undertaken a cumulative assessment. In these cases, the assessments must be applicable to the Canadian context and consistent with current policy.

A narrative is provided below to illustrate levels of refinement in both the hazard and exposure components of an assessment. The content of each tier is not meant to be prescriptive or fixed but is intended to show the progressive steps that could be undertaken in an analysis.

5.1 Hazard Assessment

At the least refined level (Tier 0), it is assumed that all chemicals in a common mechanism group have the same potency and the point of departure of the most potent member of the group is used in the assessment. This assumption, while conservative, can be used as an initial screening method to determine if further refinement is necessary and if so, to what degree. Similarly, selecting the lowest point of departure for a chemical, rather than the most relevant point of departure, can be used at an early screening stage.

At the next level of refinement (Tier 1), information on each of the chemicals in the common mechanism group can be integrated into the assessment to provide relative measures of potency. Points of departure such as the NOAELs or LOAELS for the apical effect of the individual chemicals can be used.

At a higher tier of refinement (Tier 2), additional refinements can be made incorporating information on mode of action where available. The use of benchmark dosing can allow for a more refined comparison of potencies in that it can determine the dose associated with defined response level (for example, a 10% change in the parameter of interest) for each chemical of the common mechanism group. This facilitates the comparison of potency of each chemical against an index chemical in the common mechanism group, which is then expressed as an equivalent of the index chemical or relative potency factor.

At the highest level of refinement (Tier 3), analyses can be quite sophisticated and include further consideration of mode of action data, toxicokinetics and toxicodynamics. Data modelling and probabilistic techniques can be employed although the extent of these advanced analyses will depend on the data availability, quality, strength and reliability.

5.2 Exposure Assessment

At the least refined level (Tier 0), it is assumed that exposure is based on simple semi-quantitative estimates of exposure. Semi-quantitative estimates are based on limited data and a few very simple assumptions to determine a worst-case scenario. Similarly, determining a best-case scenario can be used at an early screening stage.

At the next level of refinement (Tier 1), generic exposure scenarios are assessed using conservative point estimates. This assumption provides a conservative risk assessment in the absence of more specific, reliable exposure data, addressing a range of similar uses with limited numbers of parameters being included. However, if the risk estimates from these conservative assumptions are considered acceptable, no further evaluation is necessary.

At the next level of refinement (Tier 2), chemical-specific and more detailed and reliable data for key parameters in conjunction with risk mitigation factors are incorporated to refine the exposure risk assessment. Although still conservative, this results in more realistic exposure estimates.

At the highest level of refinement (Tier 3), data modelling and probabilistic techniques can be employed. This approach requires representative information on exposure for the scenarios of interest, and for the relevant populations and different uses across populations. The extent of these advanced analyses will depend on the data availability, quality, strength, and reliability.

6.0 Risk Characterization

In case studies undertaken by the WHO/IPCS, it has been demonstrated that refinements in the exposure assessment lead to the largest gains in characterizing risk (Meek, 2013). There is likely to be a greater difference between the lower and upper tiers of exposure assessment than there is for the tiers of hazard assessment, due to the higher reliance on assumptions in the exposure assessment. Hazard refinement, particularly at the uppermost tier, is more constrained by the absence of data on mode of action or toxicokinetics and toxicodynamics.

In assessing cumulative exposure, it is appropriate to integrate only those exposures that are likely to co-occur within the critical time window for the common toxicological effect. The challenges posed by complex exposure scenarios require approaches that allow the assessment of the effects of multiple chemicals via multiple routes and exposure pathways, and over multiple time frames. Risk assessments should consider all sources, pathways, and routes of exposure that could contribute materially to a person's total exposure.

Given the complexity of cumulative risk assessment, the characterization of risk is of utmost importance. Each assessment must clearly identify the pesticides and exposure scenarios addressed, the types and quality of data available, and the methods of estimation. It is critical that the strengths, and limitations associated with the data and analyses be discussed together with the uncertainties and assumptions. The overall level of risk can be expressed in different ways, depending on whether deterministic or probabilistic methods were used, and can reflect a series or range of estimates in light of the numerous input parameters in the assessment. These risk estimates can be specific to different age groups, durations of exposure and/or geographic regions where data permits. The target against which the cumulative risk estimates are compared should incorporate uncertainty factors that represent the cumulative assessment group as a whole (such as the factors for interspecies extrapolation and intraspecies variability) as well as the PCPA factor.

Acceptability of cumulative risk estimates must also take into account direction and magnitude of bias in the data and confidence in the data. Sensitivity analyses can assist in determining the impact of various parameters in the assessment and can contribute to the development of risk mitigation options by identifying drivers of risk.

In those cases where PMRA has leveraged a cumulative assessment from another jurisdiction, a narrative that characterizes the risk and its acceptability in the Canadian context is vital. Regardless of the approach utilized, cumulative assessments will be subject to consultation prior to final decisions as per established processes; accordingly, it is imperative that the assessments are transparent and clearly communicated.

7.0 Uncertainties and Challenges

Cumulative risk assessment represents a complex series of analyses; as such, varying degrees of uncertainty are unavoidable. These sources of uncertainty can be generic or chemical-specific.

In the case of the hazard assessment, generic sources of uncertainty can include the assumptions of dose-additivity or similar-shaped dose-response curves of chemicals within a common mechanism group and the lack of data on mode of action. Chemical-specific sources of uncertainty in hazard assessment can include the adequacy of the toxicological data to define appropriate points of departure (that is, points of departure that are temporally relevant, age relevant etc.) as well as lack of knowledge regarding human relevance.

Uncertainties in the cumulative exposure assessment include, but are not limited to, the following:

- the level of accuracy with which exposure to different chemicals can be characterised;
- the degree of understanding on the extent and profile of co-exposure to different chemicals. Different chemicals have different persistence in the environment and in the body, and therefore duration of exposure will vary; in other words, it may be episodic for one chemical and continuous for another; and
- the variability and uncertainty within the algorithms used to estimate exposure, which is compounded across substances in a cumulative context and may lead to overestimates of exposure.

8.0 Conclusions

Cumulative risk assessment methodology is a rapidly developing field as more regulatory authorities incorporate cumulative assessment into their practices. It is expected that methodology will continue to evolve with increased experience in conducting cumulative risk assessment; hence, the current framework is considered as a starting point upon which the methodology will be further developed as approaches and scientific understanding progress.

9.0 Next Steps

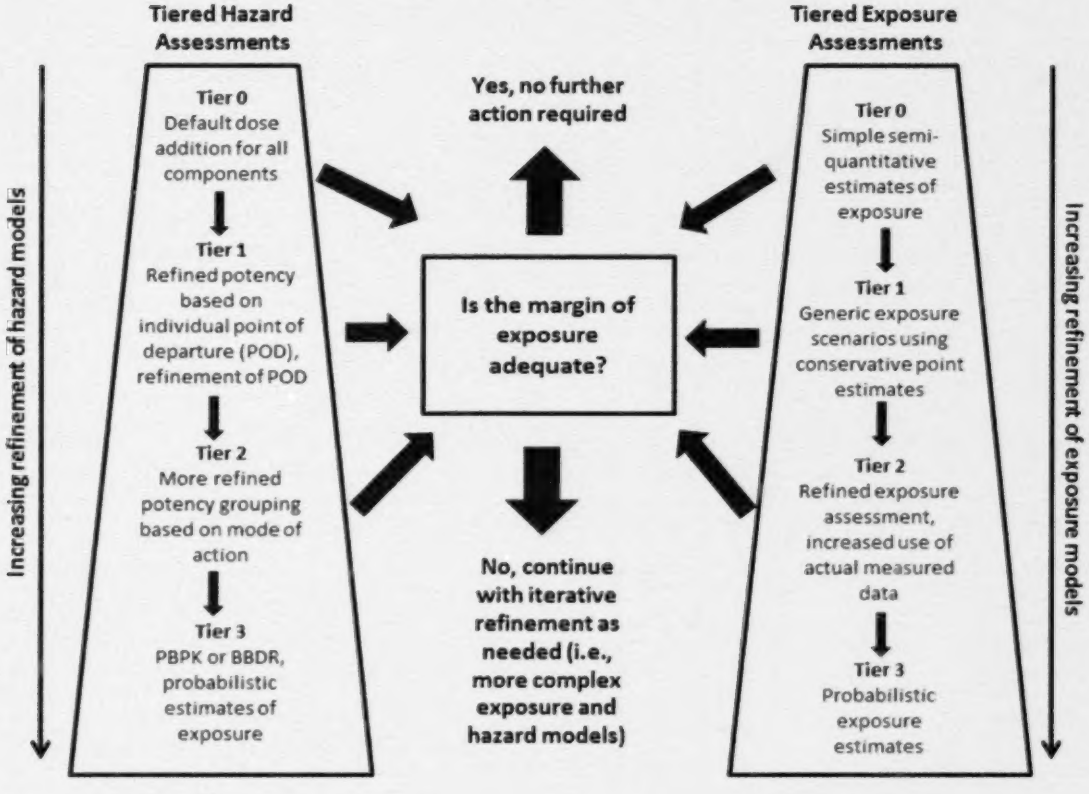
Before making a final decision on the proposed framework, the PMRA will consider any comments received from the public in response to this document. The PMRA will then publish the assessment framework, a summary of comments received on the proposed framework and the PMRA response to these comments.

Appendix I WHO/IPCS Framework for Risk Assessment of Combined Exposure to Multiple Chemicals (modified from M.E. Meek et al., (2011) Regulatory Toxicology and Pharmacology, 60: S1-S14).

Problem Formulation: Cumulative Risk Assessment

- What is the nature of exposure?
- Is exposure likely, taking into account the context?
- Is there a likelihood of co-exposure within a relevant timeframe?
- What is the rationale for considering compounds in an assessment group?

Tiered Exposure and Hazard Considerations


Tiered Hazard Assessments
Tier 0
Default dose addition for all components
Tier 1
Refined potency based on individual point of departure (POD), refinement of POD
Tier 2
More refined potency grouping based on mode of action
Tier 3
PBPK or BBDR, probabilistic estimates of exposure
Increasing refinement of hazard models
Yes, no further action required
Is the margin of exposure adequate?
No, continue with iterative refinement as needed (i.e., more complex exposure and hazard models)
Tiered Exposure Assessments
Tier 0
Simple semi-quantitative estimates of exposure
Tier 1
Generic exposure scenarios using conservative point estimates
Tier 2
Refined exposure assessment, increased use of actual measured data
Tier 3
Probabilistic exposure estimates
Increasing refinement of exposure models

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Glossary

Adverse Outcome Pathway: A linear representation of key events between a molecular initiating event and an adverse outcome

Analog(s): A generic term used to describe chemicals that are chemically closely related. Structural analogs are chemicals that have similar or nearly identical molecular structures. Structural analogs may or may not have similar or identical biological properties.

Common Mechanism Group (CMG): Pertains to two or more chemicals that cause a common toxic effect to human health by the same, or essentially the same, sequence of major biochemical events. Hence, the underlying basis of the toxicity is the same, or essentially the same, for each chemical.

Common Toxic Effect: Two or more chemicals that are known to cause the same toxic effect (that is, concordant in the nature of the effect) in or at the same anatomical or physiological site or location (for example, same organ or tissue).

Cumulative Assessment Group (CAG): Two or more chemicals grouped together for evaluation.

Cumulative Toxic Effect: The net change in magnitude of a common toxic effect resulting from the exposure to two or more chemicals acting by a common mechanism, relative to the magnitude of the common toxic effect caused by exposure to any of the chemicals individually.

Lower Confidence Limit on a Benchmark Dose (BMDL): The lower confidence limit on a benchmark dose. The benchmark dose is the dose or concentration that corresponds with a specified level of response. Both the benchmark dose and its lower limit are derived through statistical modelling of dose-response data.

Lowest Observed Adverse Effect Level (LOAEL): The lowest level of exposure in an organism that causes an adverse alteration of morphology, function, capacity, growth, development or lifespan.

Mechanism of Toxicity or Action: The molecular sequence of events that produces a specific biological outcome.

Mode of Action (MOA): A plausible hypothesis about measurable key events by which a chemical exerts it biological effects. It does not imply full understanding of mechanism of action at the molecular level. In the context of this document, mode of action refers to the key cytological and biochemical events by which a pesticide is toxic to humans or experimental animals, and not the mode of action by which it is toxic to target or intended species (that is, its pesticidal action).

No Observed Adverse Effect Level (NOAEL): A level of exposure in an organism at which there is no biologically or statistically significant increase in the frequency or severity of an adverse effect.

Point of Departure (POD): A dosage or concentration of a single chemical used in regulatory toxicology for estimating tolerable exposures to humans. The point of departure is typically based on a NOAEL, NOAEC or benchmark dose.

Site of Toxic Action: The anatomical or physiological site(s) or location(s) at which the interaction of the chemical with its biological targets occurs that leads to a toxic effect.

Site of a Toxic Effect: The specific anatomical or physiological site or location (e.g., organ or tissue) at which the effect occurs.

Toxic Action: The interaction of a given chemical with biological targets that leads to a toxic effect.

Toxic Effect: An effect known (or can reasonably be expected) to occur from exposure to a chemical and that will or can reasonably be expected to endanger or adversely affect the quality of life. Some examples of toxic effects are acute lethality, loss of hearing, renal tubule necrosis, and cardiomyopathy.

Toxophore: A structural feature or moiety that bestows the toxic property through interaction with a molecular site (e.g., receptor) in cells of tissue or organs. The resulting biochemical changes or alterations lead to the disruption of physiological processes performed by the tissue or organs and, ultimately, to the toxic effect. The toxophoric portion of a chemical may interact reversibly or irreversibly with its molecular site, depending upon its reactivity and the molecular site. For some chemicals, toxicity results from the metabolism of a structural substituent to a toxophore. Metabolic pathways that lead to toxicity are often called bioactivation pathways.

Weight-of-Evidence (WOE): A qualitative evaluation that takes into account the nature and quality of scientific information regarding a chemical for a specific purpose. A weight-of-evidence evaluation can involve a detailed analysis of several data elements, such as data from different toxicity tests, pharmacokinetic data, and chemistry data, followed by a conclusion in which a hypothesis is developed or selected from previous hypotheses.